#14

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: J. M. Steinke, A.P. Shepherd	Examiner: K. Hantis
Serial No.: 07/953,680	Group Art Unit: 2505
Filed: September 29, 1992	
For: METHOD AND APPARATUS FOR DIRECT SPECTROPHOTOMETRIC MEASUREMENTS IN UNALTERED WHOLE BLOOD	Atty. Dkt.: UTSK:142/BAH

CERTIFICATE OF MAILING
37 C.F.R. § 1.8

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as First Class Mail in an envelope addressed to: The Commissioner of Patents and Trademarks, Washington, D.C. 20231, on the date below:

December 15, 1994 — **David D. Bahler**
Date

DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

I, PER ÅKE ÖBERG, a citizen of Sweden, hereby declare and state:

1. The Chalmers Institute of Technology, Göteborg, Sweden, conferred an M.S. on me in 1964, and Uppsala University conferred a Ph.D. degree on me in 1979. These degrees are in electrical engineering and physiology, respectively.

2. From 1963 until 1972, I was affiliated with the University of Upsala, Sweden, where I lectured on medical biophysics, electronics, and control theory. Since 1972, I have been affiliated with Linköping University, Linköping, Sweden, where I hold the positions of Director of the Clinical Engineering Department of University Hospital and Full Professor of Biomedical Engineering at Linköping University.

3. I am an Elected Fellow of both the Swedish Academy of Sciences (since 1987) and the Royal Swedish Academy of Engineering Sciences (since 1980), and I have received other distinctions and scientific prizes for my contributions to biomedical engineering.

4. I am the inventor of record on a number of U.S. and foreign patents. Some of my inventions exploit the optical properties of biological tissues. Examples are "Method and Apparatus for Measuring Flow Motions in Fluid" (U.S. Patent No. 4,476,875), and "An Optical Method for Simultaneous Monitoring of Heart- and Respiration Frequency" (U.S. Patent Application No. 07/920,274).

5. I have read the following documents:

a. the above-identified U.S. patent application, including pending claims 1-36;

b. the Office Action mailed by the United States Patent and Trademark Office on October 1, 1993;

c. the reference used by the Examiner to reject claims 1-36, namely Anderson and Sekelj, "Light-absorbing and Scattering Properties of Non-Haemolysed Blood," *Phys. Med. Bio.*, vol. 12, 2:173-184, 1967;

d. the Office Action mailed by the United States Patent and Trademark Office on July 15, 1994; and

e. the U.S. patent that the Examiner used to reject claims 11-19 and 29-33, namely Curtis, U.S. Patent No. 5,064,282.

6. The Office Action of July 15, 1994, on page 7 states that Curtis ". . . in an unaltered whole blood analysis system, disclose everything except selecting four radiation wavelengths." In my view, the patent of Curtis (U.S. Patent No. 5,064,282) is a very conventional method for measuring hemoglobin because it depends entirely on hemolysis to eliminate light scattering before the sample is subjected to simple spectrophotometric analysis. Curtis states explicitly that prior hemolysis of the sample is a necessary and essential step in his method. Specifically, col. 2, line 4 reads "The only reagent required is a lysing agent which breaks up the erythrocytes to release the hemoglobin." Similarly, col. 5, line 45 states ". . . the only reagent required is saponin, a natural substance which acts as a lysing agent and breaks up the erythrocytes . . . ." By contrast, the present application of Steinke *et al.* makes it possible to make multiple spectrophotometric measurements directly in unaltered whole blood with its erythrocytes intact.

In contradiction to the Examiner's assertion, Curtis has not solved, or even attempted to solve, the problem of making spectrophotometric measurements directly in unaltered whole blood, as the invention of Steinke *et al*. does in a truly original and novel way.

7. To distinguish further the method of Curtis from that of the present application, I now cite col. 5, line 48 of Curtis: "In use, a drop of blood is placed on a glass slide, a stick having saponin thereon is stirred with the blood until translucent . . . ." In my opinion, anyone who deals with blood samples knows that stirring a thin layer of blood on a glass slide with a stick soaked in saponin alters the blood drastically and in two obvious ways. First, as mentioned previously, the saponin ruptures the red blood cells and eliminates the light scattering they cause, as confirmed by the "translucent" appearance. Second, stirring a thin layer of blood on a glass slide oxygenates the sample and thus converts some of the other hemoglobin species to oxyhemoglobin. This chemical conversion of some of the various hemoglobin species to a single species destroys the original composition so that the original concentrations of the individual hemoglobin species can no longer be determined. By contrast, the invention of Steinke *et al*. enables the measurement of not only total hemoglobin but also the relative concentrations of up to five individual hemoglobin species.

8. The Office Action of July 15, 1994, on page 7 states that "minimization of radiation scattering are [sic] disclosed by Curtis." This too is an incorrect assertion. As the application of Steinke *et al.* discloses, the turbidity of a hemolyzed blood sample is at least an order of magnitude less than the light scattering of whole blood (see Figure 2 of Steinke *et al.*). In the comparative example they offer on pages 38 through 41 of the subject patent application, Steinke *et al.* operated the Radiometer OSM3 with the ultrasonic hemolyzer turned off, and under these conditions, even this sophisticated instrument with turbidity corrections was completely incapable of yielding accurate or even plausible results (Table III, p. 39 of Steinke *et al.*). In my opinion, if truly unaltered whole blood were placed in the simple photometer of Curtis, the method of Curtis would also yield nonsensical results. The reason the method of Curtis could not possibly obtain accurate results on unaltered blood is that, contrary to the Examiner's assertion, Curtis does not disclose "minimization of radiation scattering" by any means other than prior hemolysis of the sample. Moreover, because the method of Curtis assumes that the sample has been hemolyzed, it gives no clues whatsoever as to how one would make meaningful measurements in the presence of the intense light scattering produced by unaltered whole blood.

9. The Office Action of July 15, 1994, on pages 5-6 states that "it would have been obvious to one with ordinary skill in the art

to modify Anderson to incorporate . . ." all of the following: "the specific depth of the sample, the specific detecting area, the specific distance from the sample, the specific half aperture angle of radiation emanating from the sample, computing an error index, selecting a wavelength range . . ., red blood cell scattering vector and nonspecific scattering vector." As an experienced inventor with at least ordinary skill in the art, based upon the teachings of Anderson and Sekelj, I do not have the slightest idea how to arrive at specific values for any of the foregoing factors because Anderson and Sekelj do not provide any clue or suggestion about how to do so. Furthermore, the Examiner's misconception appears to originate from the false notion on page 6 of the Office Action that "a specific relationship between all of the specifics cited above are well known . . . ." Simply reading Anderson and Sekelj will show that they do not address the specific detecting area, the specific distance from the sample, the specific half angle of radiation emanating from the sample, computing an error index, the selection of a wavelength range, a red blood cell scattering vector, or a nonspecific scattering vector. Similarly, even though Anderson and Sekelj show that optical density increases with sample depth as was already well known (Figure 3), this does not teach me personally how to select the optimum sample depth for minimal error from light scattering, nor does it teach me how to select optimum values for any of the previously mentioned instrumental parameters.

10. For example, the AVOXimeter 1000, a whole-blood oximeter now commercially available, is an embodiment of the invention of Steinke *et al.* According to the manufacturer's specifications, this device measures the percent oxyhemoglobin to an accuracy of 1% and the total hemoglobin to an accuracy of 0.45 g/dL. Nowhere in Anderson *et al.* or in any prior art of which I am aware is it taught how to select a specific sample depth to achieve a measurement with an accuracy of 1% oxyhemoglobin in unaltered whole blood. Similarly, nowhere in Anderson *et al.* or in any prior art of which I am aware is it taught how to select a specific distance from the sample to the detector. Likewise, nowhere in Anderson *et al.* or in any prior art of which I am aware is it taught how to select the instrumental parameters mentioned in paragraph 9 to achieve the performance specifications of the above-cited embodiment of the present invention.

11. On the contrary, Anderson *et al.* actually makes incorrect and misleading statements, as on page 180: "Curve (c), which shows the parabolic relationship between OD and scattering, remains the same for this sample depth and haemoglobin content when wavelength is varied. Thus, to obtain OD at 5300 Å, for example, it is necessary to change only the slope of curve (b) according to the haemoglobin ϵ at that wavelength." The present application of Steinke *et al.* shows that scattering depends very much on wavelength, thus contradicting Anderson *et al.* (see

Figures 4 and 5 of Steinke *et al.*). Therefore, scattering does not "remain the same" as Anderson *et al.* concluded. Consequently, the present application of Steinke *et al.* cannot possibly rely on Anderson's results. Furthermore, Steinke *et al.* discovered a second mathematical dimension of scattering, the "nonspecific scattering vector," which is not only wavelength dependent, but completely uncontemplated by Anderson *et al.* This is a rather surprising discovery, unknown to Anderson *et al.* and, in my opinion, unknown to anyone who has not read the present application of Steinke *et al.* The two dimensions of scattering in the application of Steinke *et al.* are independent, and in the general case, there are nonzero magnitudes of both kinds of scattering. Finally, Anderson *et al.* makes no provision whatsoever for scattering variations from sample to sample (patient-to-patient variability). Steinke *et al.* have found that scattering has different magnitudes from sample to sample, even for the same hemoglobin concentration and the same wavelength. In the present patent application, this provision is embodied through their linear algebra techniques which adequately compensate for these different scattering magnitudes. By contrast, Anderson *et al.* assumes that there is no variation in the scattering magnitude, a fundamentally incorrect assumption.

12. On page 4 of the Office Action of July 15, 1994, the Examiner mistakenly claims that Anderson and Sekelj "inherently" have "correction for calculated concentrations." The Examiner

does not realize that Anderson and Sekelj have not "calculated" the total hemoglobin concentration; they have simply measured the total hemoglobin concentration by some independent, unstated means and then used curve-fitting techniques to determine whether Twersky's equation roughly fits the optical density measured in suspensions of red blood cells in isotonic saline with various known hemoglobin concentrations. The paper by Anderson and Sekelj does not constitute a practical means of optically measuring hemoglobin concentration, nor was it meant to do so. As the authors state clearly, the purpose was merely "to investigate the light-scattering and light-absorbing properties of nonhaemolysed blood" (see page 174 of Anderson and Sekelj).

13. The Office Action of July 15, 1994, on pages 7-8 states that:

> it would have been obvious to one with ordinary skill in the art to modify Curtis to incorporate the four wavelength of Applicant's device. The rationale for this modification would have arisen since Curtis selects two wavelengths so as to minimize error due to the variations in the oxygenation, deoxygenation of the blood. It would have been obvious to modify Curtis to select four wavelengths instead of two wavelengths since the four wavelengths are used for the same reasons two wavelengths are used i.e. to reduce variations as cited above. Clearly, the interchangeability of selecting two or four wavelengths is apparent since both will produce a minimum error measurement as seen by Curtis.

This statement is completely incorrect and reveals a serious misunderstanding of Curtis' and of Steinke's wavelength selection methods. Curtis sought two wavelength passbands for which oxyhemoglobin and deoxyhemoglobin have approximately equal

absorptivity deltas (average absorptivity at passband 1 minus average absorptivity at passband 2 being approximately the same for oxy- and deoxyhemoglobin). His goal was to measure total hemoglobin concentration using only the difference in absorbance at two wavelength passbands; therefore, he was forced to seek the same delta for oxyhemoglobin and deoxyhemoglobin so that the answer he obtained for hemoglobin concentration did not depend much on the state of oxygenation of the sample. What is more, Curtis' apparatus used hemolyzed blood and therefore Curtis did not have to contend with the effects of scattering or the added variability in measured optical density which occurs when the blood is nonhemolyzed and scattering is present.

14. By contrast, Steinke *et al.*, assuming the sample to be nonhemolyzed whole blood with light scattering properties at least an order of magnitude greater than that of hemolyzed blood (Figure 2 of the present patent application), set about to minimize the error in %HbO2, %HbMet, and %HbCO that would result from errors in optical density measurements made on nonhemolyzed whole blood. They assumed that the sample's oxygenation was to be preserved; it was not allowed to change during the sampling method. Their technique resulted in checking through hundreds of thousands of quadruples of wavelengths, and inverting a matrix and computing three error criteria for each quadruple of wavelengths. By contrast, the passband selection described by Curtis can be done by a careful inspection of the graph of the

spectra of the relevant hemoglobin species. It is fairly easy to determine visually where a difference in absorptivities is approximately the same for two hemoglobin species. In conclusion, the goals of Curtis and of Steinke *et al.* were completely different, and the difficulty of their tasks was greatly different as well -- it is completely erroneous to say that "it would have been obvious to one with ordinary skill in the art to modify Curtis to incorporate the four wavelength of Applicant's device".

15. On page 9 of the Office Action of July 15, 1994, the Examiner claims that Anderson *et al.* "is measuring a plurality of constituent components of unaltered whole blood." This assertion is completely false because nowhere in Anderson *et al.* is it stated that the concentration of any hemoglobin species was determined by optical means in unaltered whole blood. As I stated above, Anderson and Sekelj already know the total hemoglobin concentrations in the red cell suspensions when they measure the optical density in their apparatus. The Examiner further contends that Anderson and Sekelj construct a "calibration curve" from which they can deduce the hemoglobin concentrations in "whole unaltered blood of unknown composition." This assertion, too, is completely false. In fact, I am convinced that if one were to proceed to construct a "calibration curve" in the manner suggested by the Examiner, the method of Anderson and Sekelj would fail to achieve the desired results.

The method of Anderson and Sekelj, if modified as suggested by the Examiner, would fail for many different reasons. For example, if a sample of blood contained 7 g/dl of oxyhemoglobin and 7 g/dl of carboxyhemoglobin, which of Anderson's calibration curves would be used, and how would they be used to determine the concentration of both oxyhemoglobin and carboxyhemoglobin in that sample? What if the sample of unaltered whole blood contained 1 g/dl of methemoglobin, 2 g/dl of carboxyhemoglobin, 3 g/dl of reduced hemoglobin, 4 g/dl of oxyhemoglobin? The so-called "calibration curves" of Anderson *et al.* cannot be used since none of those curves represent the compositions described above, or any random compositions which may be present in whole blood.

16. In addition, it should be noted that in order to generate their curves, Anderson *et al.* must necessarily alter the hemoglobin concentration of the samples under study. According to Anderson *et al.*, altered hemoglobin concentration is accomplished by suspending fully oxygenated nonhemoglyzed red blood cells in isotonic saline (Anderson *et al.*, page 177, second paragraph). Anderson *et al.* thus contemplate only the use of altered blood, not unaltered blood as required by Steinke *et al.*

17. On page 9 of the Office Action of July 15, 1994, it is stated that the argument that "the curve-fitting techniques of Anderson are different from Applicants' device" is moot since "these differences of techniques are not claimed in Applicant's

claims." It is obvious to me that Steinke *et al.* had no need to distinguish their technique from any other technique since, in fact, there is no other technique for doing what they have done. The Office Action reveals the fundamental misunderstanding, as I have shown through this declaration, that Anderson *et al.* is actually measuring concentrations of hemoglobin species by optical means, when in fact this is simply not the case. To disregard something on the basis that "differences of techniques are not claimed in Applicant's claims" is to dismiss something on a completely false premise.

18. To the best of my knowledge, the invention of Steinke *et al.* is the only method for spectrophotometrically measuring the total hemoglobin concentration and the relative concentrations of up to five individual hemoglobin species directly in unaltered whole blood. As an expert on clinical engineering and hospital equipment, I know of no other instrument or equipment that can achieve the results of the invention of Steinke *et al.*

19. The prior art references of which I am aware, including Anderson *et al.* and Curtis, do not teach one of ordinary skill in this technology and do not teach me personally, how to make or use the invention as claimed in the above-identified U.S. patent application. Furthermore, even in view of the scope and content of the disclosure of that prior art, the invention as claimed in this application as a whole would not have been obvious at the

time the invention was made to a person having ordinary skill in this art.

20. I hereby declare that all of the statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful, false statements and the like are punishable by fine or imprisonment under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the above-identified application, or any patent issuing therefrom.

1994-12-12

Date

Per Åke Öberg

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#14

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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December 15, 1994
Date

David D. Bahler

DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

I, GERT E. NILSSON, a citizen of Sweden, hereby declare and state:

1. I received an M.Sc. degree from Lund University, Sweden, in 1972 and a Ph.D. degree in Biomedical Engineering from Linköping University, Sweden in 1977.

2. From 1980 until 1983, I was an associate professor in the department of Biomedical Engineering at Linköping University. From 1983 until 1985, I was a development manager for Gambro Cardio AB, and from 1985 until 1987, I was a development manager for Perimed AB. I am presently a professor in Biomedical Instrumentation at Linköping University and was head of the department of Biomedical Engineering, at Linköping University, from July 1990 until June 1993.

3. I was a member of the International Organizing Committee of the IEEE Biomedical Engineering Society until June, 1993.

4. During my education and work experience, I have become familiar with the mechanics of blood flow, with a particular concentration in laser Doppler flowmetry of blood. I have authored numerous publications, and am an inventor or co-inventor of several U.S. patents, and patents in other countries, in this technical area. Attached to this Declaration is a copy of my *Curriculum Vitae*, which presents a more complete version of my education, employment, publications and patents.

5. I have read the following documents:

a. the above-identified U.S. patent application, including pending claims 1-36;

b. the Office Action mailed by the United States Patent and Trademark Office on October 1, 1993;

c. the reference used by the Examiner to reject claims 1-36, namely Anderson and Sekelj, "Light-absorbing and Scattering Properties of Non-Haemolysed Blood," *Phys. Med. Bio.*, vol. 12, 2:173-184, 1967;

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In contradiction to the Examiner's assertion, Curtis has not solved, or even attempted to solve, the problem of making spectrophotometric measurements directly in unaltered whole blood, as the invention of Steinke *et al*. does in a truly original and novel way.

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to modify Anderson to incorporate . . ." all of the following: "the specific depth of the sample, the specific detecting area, the specific distance from the sample, the specific half aperture angle of radiation emanating from the sample, computing an error index, selecting a wavelength range . . ., red blood cell scattering vector and nonspecific scattering vector." As an experienced inventor with at least ordinary skill in the art, based upon the teachings of Anderson and Sekelj, I do not have the slightest idea how to arrive at specific values for any of the foregoing factors because Anderson and Sekelj do not provide any clue or suggestion about how to do so. Furthermore, the Examiner's misconception appears to originate from the false notion on page 6 of the Office Action that "a specific relationship between all of the specifics cited above are well known . . . ." Simply reading Anderson and Sekelj will show that they do not address the specific detecting area, the specific distance from the sample, the specific half angle of radiation emanating from the sample, computing an error index, the selection of a wavelength range, a red blood cell scattering vector, or a nonspecific scattering vector. Similarly, even though Anderson and Sekelj show that optical density increases with sample depth as was already well known (Figure 3), this does not teach me personally how to select the optimum sample depth for minimal error from light scattering, nor does it teach me how to select optimum values for any of the previously mentioned instrumental parameters.

10. For example, the AVOXimeter 1000, a whole-blood oximeter now commercially available, is an embodiment of the invention of Steinke *et al.* According to the manufacturer's specifications, this device measures the percent oxyhemoglobin to an accuracy of 1% and the total hemoglobin to an accuracy of 0.45 g/dL. Nowhere in Anderson *et al.* or in any prior art of which I am aware is it taught how to select a specific sample depth to achieve a measurement with an accuracy of 1% oxyhemoglobin in unaltered whole blood. Similarly, nowhere in Anderson *et al.* or in any prior art of which I am aware is it taught how to select a specific distance from the sample to the detector. Likewise, nowhere in Anderson *et al.* or in any prior art of which I am aware is it taught how to select the instrumental parameters mentioned in paragraph 9 to achieve the performance specifications of the above-cited embodiment of the present invention.

11. On the contrary, Anderson *et al.* actually makes incorrect and misleading statements, as on page 180: "Curve (c), which shows the parabolic relationship between OD and scattering, remains the same for this sample depth and haemoglobin content when wavelength is varied. Thus, to obtain OD at 5300 Å, for example, it is necessary to change only the slope of curve (b) according to the haemoglobin ϵ at that wavelength." The present application of Steinke *et al.* shows that scattering depends very much on wavelength, thus contradicting Anderson *et al.* (see

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does not realize that Anderson and Sekelj have not "calculated" the total hemoglobin concentration; they have simply measured the total hemoglobin concentration by some independent, unstated means and then used curve-fitting techniques to determine whether Twersky's equation roughly fits the optical density measured in suspensions of red blood cells in isotonic saline with various known hemoglobin concentrations. The paper by Anderson and Sekelj does not constitute a practical means of optically measuring hemoglobin concentration, nor was it meant to do so. As the authors state clearly, the purpose was merely "to investigate the light-scattering and light-absorbing properties of nonhaemolysed blood" (see page 174 of Anderson and Sekelj).

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This statement is completely incorrect and reveals a serious misunderstanding of Curtis' and of Steinke's wavelength selection methods. Curtis sought two wavelength passbands for which oxyhemoglobin and deoxyhemoglobin have approximately equal

absorptivity deltas (average absorptivity at passband 1 minus average absorptivity at passband 2 being approximately the same for oxy- and deoxyhemoglobin). His goal was to measure total hemoglobin concentration using only the difference in absorbance at two wavelength passbands; therefore, he was forced to seek the same delta for oxyhemoglobin and deoxyhemoglobin so that the answer he obtained for hemoglobin concentration did not depend much on the state of oxygenation of the sample. What is more, Curtis' apparatus used hemolyzed blood and therefore Curtis did not have to contend with the effects of scattering or the added variability in measured optical density which occurs when the blood is nonhemolyzed and scattering is present.

14. By contrast, Steinke *et al.*, assuming the sample to be nonhemolyzed whole blood with light scattering properties at least an order of magnitude greater than that of hemolyzed blood (Figure 2 of the present patent application), set about to minimize the error in %HbO2, %HbMet, and %HbCO that would result from errors in optical density measurements made on nonhemolyzed whole blood. They assumed that the sample's oxygenation was to be preserved; it was not allowed to change during the sampling method. Their technique resulted in checking through hundreds of thousands of quadruples of wavelengths, and inverting a matrix and computing three error criteria for each quadruple of wavelengths. By contrast, the passband selection described by Curtis can be done by a careful inspection of the graph of the

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The method of Anderson and Sekelj, if modified as suggested by the Examiner, would fail for many different reasons. For example, if a sample of blood contained 7 g/dl of oxyhemoglobin and 7 g/dl of carboxyhemoglobin, which of Anderson's calibration curves would be used, and how would they be used to determine the concentration of both oxyhemoglobin and carboxyhemoglobin in that sample? What if the sample of unaltered whole blood contained 1 g/dl of methemoglobin, 2 g/dl of carboxyhemoglobin, 3 g/dl of reduced hemoglobin, 4 g/dl of oxyhemoglobin? The so-called "calibration curves" of Anderson *et al.* cannot be used since none of those curves represent the compositions described above, or any random compositions which may be present in whole blood.

16. In addition, it should be noted that in order to generate their curves, Anderson *et al.* must necessarily alter the hemoglobin concentration of the samples under study. According to Anderson *et al.*, altered hemoglobin concentration is accomplished by suspending fully oxygenated nonhemoglyzed red blood cells in isotonic saline (Anderson *et al.*, page 177, second paragraph). Anderson *et al.* thus contemplate only the use of altered blood, not unaltered blood as required by Steinke *et al.*

17. On page 9 of the Office Action of July 15, 1994, it is stated that the argument that "the curve-fitting techniques of Anderson are different from Applicants' device" is moot since "these differences of techniques are not claimed in Applicant's

claims." It is obvious to me that Steinke *et al.* had no need to distinguish their technique from any other technique since, in fact, there is no other technique for doing what they have done. The Office Action reveals the fundamental misunderstanding, as I have shown through this declaration, that Anderson *et al.* is actually measuring concentrations of hemoglobin species by optical means, when in fact this is simply not the case. To disregard something on the basis that "differences of techniques are not claimed in Applicant's claims" is to dismiss something on a completely false premise.

18. To the best of my knowledge, the invention of Steinke *et al.* is the only method for spectrophotometrically measuring the total hemoglobin concentration and the relative concentrations of up to five individual hemoglobin species directly in unaltered whole blood. As an expert on clinical engineering and hospital equipment, I know of no other instrument or equipment that can achieve the results of the invention of Steinke *et al.*

19. The prior art references of which I am aware, including Anderson *et al.* and Curtis, do not teach one of ordinary skill in this technology and do not teach me personally, how to make or use the invention as claimed in the above-identified U.S. patent application. Furthermore, even in view of the scope and content of the disclosure of that prior art, the invention as claimed in this application as a whole would not have been obvious at the

time the invention was made to a person having ordinary skill in this art.

20. I hereby declare that all of the statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful, false statements and the like are punishable by fine or imprisonment under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the above-identified application, or any patent issuing therefrom.

1994-12-08
Date

Gert E. Nilsson

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LIST OF QUALIFICATIONS
for
Gert Erik Nilsson

Gert Erik Nilsson, born June 12, 1947, in Malmö, Sweden.

A. EDUCATION.

1. Undergraduate exam from Johannes kommunala gymnasium in Malmö 1966.
2. University studies in mathematics at Lunds University, 1967.
3. University studies in theorethical physics at Lund University, 1967.
4. Master of Science at The University of Lund (electrotechnology), 1972.
5. Basic training courses in biochemistry, physiology, medicine, medical informatics and biomedical engineering at Linköping University, 1972-1975.
6. PhD-degree in biomedical engineering from Linköping University, 1977.
7. Associate professor in biomedical engineering at Linköping University, 1980.
8. Management training courses, Gambro AB, 1984.
9. Training course in project management, 1988.

B. EMPLOYMENTS.

1. Assistant at the department of biomedical engineering, Linköping University, Linköping, Sweden, 1972-1974.
2. Research engineer at the department of biomedical engineering, Linköping University, Linköping, Sweden, 1974-1977.
3. Research assistant at the department of biomedical engineering, Linköping University, Linköping, Sweden, 1977-1980.
4. Researcher at the department of biomedical engineering, Linköping University, Linköping, Sweden, 1980-1982.
5. Holding office professor at the department of biomedical engineering, Linköping University, Linköping, Sweden, 1982-1983.
6. Development manager at Gambro Cardio AB, 1983-1985.
7. Independent consultant, 1985-1987.
8. Professor in Biomedical instrumentation at Linköping University since July 1, 1987.
9. Head of the department of biomedical engineering, Linköping University, Linköping, Sweden, since July 1, 1990.

C. OTHER TEACHING DUTIES.

1. Assistant at the department of informatics, University of Lund, 1970-1971.

2. Assistant at the department of theoretical electrotechnology, University of Lund, 1971-1972.

3. Superviser for undergraduate student projects at the department of biomedical engineering, Linköping University, 1974-1982.

4. Lecturer in biomedical engineering, Linköping University, 1974-1980.

5. Lecturer in medical specialist training courses in anesthesiology and clinical physiology, Linköping University Hospital, 1973-1981.

6. Lecturer in fine mechanics at Linköping University, 1977-1981.

7. Supervisor in the PhD-training program at the department of biomedical engineering, Linköping University, 1977-1982.

D. INDUSTRIAL COMMISSIONS

1. Consultant for Farad AB, Stockholm, within the area of biological activity measurements, 1971.

2. Active in the Swedish Board of Technical Development project "Development of a system for the assessment of water evaporation from the skin and respiratory tract", 1974-1977. The project resulted in a commercial product (The Evaporimeter), which is marketed by ServoMed AB, Stockholm. The project involved elements of transferring a prototype into industrial production.

3. Consultant for ServoMed AB, 1977-1982 for application research and market introduction of the Evaporimeter.

4. Project manager for the project "Development of a heat radiation ceiling for treatment of burned patients". The project resulted in a commercial product (The OPN-ceiling), available through Aragona AB, Stockholm.

5. Consultant for Aragona AB 1979-1980 for the industrial adaptation and clinical evaluation of the OPN-ceiling.

6. Project manager in the Swedish Board of Technical development project "Technical methods for the assessment of peripheral circulation", 1978-1983. The project resulted in a commercially available product (Periflux laser Doppler flowmeter) marketed by Perimed AB, Stockholm. This company was founded by Sven Malmström, Åke Öberg, Torsten Tenland and myself in 1980. Among other things the project included elements of adaptation of a prototype for industrial production, clinical evaluation and preparations for manufacturing in serial production.

7. Consultant for Perimed KB, Stockholm, 1980-1983 for adaptation and market introduction of the Periflux PF1 laser Doppler flowmeter. Among other activities the task involved the training of a sales force in Europe and Japan.

8. Project manager for The Swedish Defense Research project "Technical methods for the assessment of the microclimate of the skin", 1981-1983.

9. Development manager at Gambro Cardio AB (heart-lung machines), Lund, 1983-1985.

10. Responsible (as consultant) for the development of the laser Doppler flowmeter Periflux PF3, and for the introduction of this device on the US market, 1985 - 1987.

11. Member of the board of directors of Perimed AB 1982-1991.

12. Chairman of the board of Lisca Development AB (imaging systems), Linköping, since March 1991.

E. PATENTS.

1. Within the area of biological activity measurment (USA and Germany).

2. Within the area of measurement of evaporative water loss (England, France, Holland, Sweden and USA).

3. Within the area of measurement of tissue blood flow by a laser Doppler technique (England, France, Holland, Japan, Sweden and USA).

4. Within the area of signal processing in laser Doppler flowmetry (Sweden and USA).

5. Within the area of laser Doppler perfusion imaging. Patent pending in Sweden, USA, Japan, Germany, England, France and Italy.

6. Within the area of distance dependence compensation for laser Doppler perfusion imaging. Patent pending in Sweden, USA, Japan, Germany, England, France and Italy.

F. OTHER MERITS.

1. Declared competent as general manager of the biomedical engineering unit, Malmöhus läns landsting, 1978.

2. Declared competent as professor in medical electronics, Chalmers tekniska högskola, 1981.

3. Chairman of Östergötlands tekniska förening, biomedical engineering division, 1978-1981.

4. Member of the board of directors, Perimed KB, 1982-1983.

5. Member of the National Swedish board of technical development working party for peripheral circulation, 1978-1983.

6. Member of the technical faculty board, Linköping University, 1977-1980, deputy member 1980-1982.

7. Member of the technical faculty board, Linköping University, 1982-1983.

8. Recepient of the Arnberg's award from The Royal Swedish Academy of Science1986, for contributions to the field of biomedical engineering.

9. Faculty opponent at Lund University, 1986.

10. Recepient of the Erna Ebeling's award, 1986, for contributions to the field of biomedical engineering.

11. Scientific secretary in The Swedish society for medical engineering and physics, 1987-1988.

12. Faculty opponent at Oslo University, 1988.

13. Organizer for The Swedish society for medical engineering and physics "biomedical engineering day", 1988. (Topic: Biomedical ultrasonic and laser equipment).

14. Invited key-note speaker at the 3rd autumn meeting of JMEBE, Tokyo, 1988.

15. Member of the IEEE's international committee for organization of annual MBSE-conferences since 1989.

16. Organizer of the scientific session at The Swedish society for medical engineering and physics meetings, 1988-1989.

17. Organizer for The Swedish society for medical engineering and physics "biomedical engineering day", 1989 (Topic: PACS systems).

18. Expert at the assessment of ass. prof. Håkan Håkanssons appointment as assistant proffesor in Biochemical Instrumentation at the University of Lund, 1989.

19. Recepient of the Innovation Cup award for "Development of an imaging system for the assessment of microcirculation", 1989.

20. Organizer for The Swedish society for medical engineering and physics "biomedical engineering day", 1989 (Topic: Biosensor technology).

21. Organizer of a Training Course in the use of laser Doppler flowmetry, London 4 - 5 juli, 1992.

G. ORIGINAL PAPERS.

1. NILSSON, G. Measurement of the water exchange through the skin. *Med and Biol Eng & Comput., 15, p209-218, 1977.*

2. LAMKE, L-O., NILSSON, G. & REITHNER, H.L. The evaporative waterloss from burns and the water vapour permeability of grafts and artificial membranes used in the treatment of burns. *Burns, vol 3,No 3, p159-165., 1977.*

3. NILSSON, G. On the measurement of Evaporative Water Loss. *Akademisk avhandling, Linköping 1977.*

4. LAMKE, L-O., NILSSON, G. & REITHNER, H.L. Insensible perspiration from the skin under standardized environmental conditions. *Scand J Clin & Lab Invest. 37, p325-331, 1977.*

5. HAMMARLUND, K., NILSSON, G., SEDIN, G. & ÖBERG, P-Å. Transepidermal water loss in newborn infants I: Relation to ambient humidity and site of measurement, and estimation of total transepidermal water loss. *Acta Paediatr Scand. 66, p553-562, 1977.*

6. LAMKE, L-O., NILSSON, G. & REITHNER, H.L. Water loss by evaporation from the abdominal cavity during surgery. *Acta Chir Scand 143, p279-284, 1977.*

7. NILSSON, G., TENLAND, T. & ÖBERG, P-Å. A new Instrument for continuous measurement of tissue blood flow by light beating spectroscopy. *IEEE Trans on Biomed Eng Vol BME-27, No 1, 1980.*

8. ÖBERG, P-Å., NILSSON, G., TENLAND, T., HOLMSTRÖM, A. & LEWIS, D. Use of a new laser Doppler flowmeter for measurement of capillary blood flow in skeletal muscle after bullet wounding. *Acta Chir Scand. Suppl. 489, p145-150, 1979.*

9. LAMKE, L-O., NILSSON, G.E. & REITHNER, H.L. The influence of body temperature on skin perspiration. *Acta Chir Scand. 146, p81-84,1980.*

10. HAMMARLUND, K., NILSSON, G.E., ÖBERG, P-Å. & SEDIN, G. Transepidermal water loss in newborn infants II: Relation to activity and body temperature. *Acta Paed Scand. 68, p371-376, 1979.*

11. NILSSON, A.L., NILSSON, G.E. & ÖBERG, P-Å. A note on periodic sweating. *Acta Phys Scand 108, p189-190, 1980.*

12. HAMMARLUND, K., NILSSON, G.E., ÖBERG, P-Å. & SEDIN, G. Transepidermal water loss in newborn infants V: Evaporation from the skin and heat exchange during the first hours of life. *Acta Paed Scand. 69, p385-392, 1980.*

13. NILSSON, G.E., TENLAND, T. & ÖBERG, P-Å. Evaluation of a laser Doppler flowmeter for measurement of tissue blood flow. *IEEE Trans on Biomed Eng. Vol BME-27, No 10, 1980.*

14. NILSSON, A.L., NILSSON, G.E. & ÖBERG, P-Å. On periodic sweating from the human skin during rest and exercise. *Acta Phys Scand.114, p567-571, 1982.*

15. NILSSON, G.E., OTTO, U. & WAHLBERG, J.E. Assessment of skin irritancy in man by laser Doppler flowmetry. *Contact Dermatitis. 8, p401-406, 1982.*

16. BENGTSSON, M., NLSSON, G.E. & LÖFSTRÖM, J.B. The effect of spinal analgesia on skin blood flow, evaluated by laser Doppler flowmetry. *Acta Anaesth Scand 27, p206-210, 1983.*

17. SALERUD, G.E., TENLAND, T., NILSSON, G.E. & ÖBERG, P-Å. Rhythmical variations in human skin blood flow. *Int J Microcirc: Clin Exp2, p91-102, 1983.*

18. TENLAND, T., SALERUD, G.E., NILSSON, G.E. & ÖBERG, P-Å. Spatial and temporal variations in human skin blood flow. *Int J Microcirc: Clin Exp 2, p81-90, 1983.*

19. HELLEM, S., JACOBSSON, L.S., NILSSON, G.E. & LEWIS, D.H. Measurement of microvascular blood flow in cancellous bone using laser Doppler Flowmetry and Xe-clearance. *In J Oral Surg 12: p165-177, 1983.*

20. HELLEM, S., JACOBSSON, L.S. & NILSSON, G.E. Microvascular response in cancellous bone to experimental halothane induced hypotension in pigs. *Int J Oral Surg, 12, p178-185, 1983.*

21. NILSSON, G.E. & PETTERSSON, H. Controlled radiation ceiling for thermal treatment of patients. Acta Medicotechnica, *31, No 3 p86-87, 1983.*

22. NILSSON, G.E. Signal processor for tissue laser Doppler flowmeters. *Med & Biol Engng & Comp, 22, p343-348, 1984.*

23. WAHLBERG, J.E. & NILSSON, G.E. Skin irritancy from PropyleneGlycol. *Acta Derm Venereol, 64, p286-290, 1984.*

24. AHN, H., LINDHAGEN, J., NILSSON, G.E., SALERUD, E.G., JODAL, M. & LUNDGREN, O. Evaluation of Laser Doppler Flowmetry in the Assessment of Intestinal Blood Flow in Cat. *Gastroenterology, 88, p951-957, 1985.*

25. SALERUD, E.G. & NILSSON, G.E. Integrating probe for tissue laser Doppler flowmeters. *Med & Biol Engng & Comput,* **24,** *p415-419, 1986.*

26. AHN, H., LINDHAGEN, J., NILSSON, G.E., ÖBERG, P-Å. & LUNDGREN, O. Assessment of Blood Flow in the Small Intestine with Laser Doppler Flowmetry. *Scand J Gastroenterol, 21, p863-870, 1986.*

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29. AHN, H., EKROTH, R., NILSSON, G.E. & SVEDJEHOLM, R. Assessment of myocardial perfusion with laser Doppler flowmetry an experimental study on the porcine heart. *Scand J Thor Cardiovasc Surg 22:145-148, 1988.*

30. AHN, H., EKROTH, R., NILSSON, G.E., SVEDJEHOLM, R. Laser Doppler Flowmetry estimating myocardial perfusion after internal mammary grafting. *Scand J Thor Cardiovasc Surg 22: 281-284, 1988.*

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32. NILSSON. A.L., ERIKSSON, L.E. and NILSSON, G.E. Effects of local cooling and rewarming on skin blood flow. *Int J Microcirc: Clin Exp5:11-25 (1986).*

33. JOHANSSON, K., JAKOBSSON, A., LINDAHL, K., LINDHAGEN, J., LUNDGREN,O. and NILSSON, G.E. Influence of fibre diameter and probe geometry on the measuring depth of laser Doppler flowmetry in the gastrointestinal application. *Int J Microcirc: Clin Exp 10:219-229 (1991).*

34. GUSTAVSSON, U., WÅRDELL, K., NILSSON, G.E. and LEWIS, D.H. Vasomotion in Rat Skeletal Muscle Induced by Hemorrhage as Recorded by Laser-Doppler Flowmetry. *Microvascular Research , 42, 224-228, 1991.*

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37. WÅRDELL, K., JAKOBSSON, A.J. and NILSSON, G.E. Laser Doppler Perfusion Imaging by Dynamic Light Scattering. *Accepted for publication in IEEE Trans on Biomedical Engineering, 1992.*

38. WÅRDELL, K., NAVER, H.K., NILSSON, G.E. and WALLIN, B.G. The cutaneous vascular axon reflex characterized by laser Doppler perfusion imaging. *Accepted for publication in Journal of Physiology, 1992.*

39. UHL, E., SIRSJÖ, A., HAAPANIEMI, T., NILSSON, G.E., MESSMER, K. and NYLANDER, G. Hyperbaric oxygen improves wound healing in normal and ischemic skin tissue. *In manuscript, 1992.*

H. CONFERENCE PAPERS.

1. NILSSON, G.E. & ÖBERG, P-Å. A new method for measurement of transepidermal water loss. III Nordic meating on medical and biological engineering. *Tampere, Finland, 1975.*

2. NILSSON, G.E. & ÖBERG, P-Å. En ny metod för kvantitativ bestämning av vattenavdunstning. *Radiovetenskaplig konferens, Linköping.1975.*

3. NILSSON, G.E., ÖBERG, P.-Å. & SEDIN, G. A transducer for measurement of evaporation from the skin. *International conference on biomedical transducers, Paris, France, 1975.*

4. LAMKE, L-O., NILSSON, G.E., REITHNER, H.L.& ÖBERG, P-Å.On the measurement of water loss from the skin and surgical wounds. *XI International conference on medical and biologicalengineering, Ottawa, Canada, 1976.*

5. NILSSON, G.E., LAMKE, L-O. & ÖBERG, P-Å. Evaporimetern - ett instrument för bestämning av vattenavdunstning. *Läkarsällskapets riksstämma, 1976.*

6. LAMKE, L-O., NILSSON, G.E. & REITHNER, H.L. Mätning av hudens perspiratio insensibilis. *Läkarsällskapets riksstämma, 1976.*

7. SEDIN, G., HAMMARLUND, K., NILSSON, G. & ÖBERG, P-Å. Evaporative water loss in full term and premature newborn infants. *6th Nordic Congress for perinatal medicine, Oulu, Finland, 1977.*

8. REITHNER, H.L., LAMKE, L-O., LILJEDAHL, S-O., NILSSON, G.E. &ÖBERG, P-Å. Apparatur för mätning av vattenavdunstning från hud och bukhåla hos kirurgiska patienter. *Sv Kirurgisk FöreningLinköping, 1977.*

9. REITHNER, H.L., LAMKE, L-O. & NILSSON, G.E. Biologiska och artificiella membraners inverkan på avdunstningen från brännskador och tagställen. *Sv Kir Förening, Linköping, 1977.*

10. REITHNER, H.L., LAMKE, L-O. & NILSSON, G.E. Perspiratio insensibilis hos kirurgiska patienter. *Läkarsällskapets riksstämma, 1977.*

11. SEDIN, G., HAMMARLUND, K., NILSSON, G.E. & ÖBERG, P-Å. The influence of environment, activity and gestational age on evaporative water loss. *European Society for Peadiatric Research,Finland, 1978.*

12. NILSSON, G.E. & ÖBERG, P-Å. An instrument for measurement of evaporative water loss. *5th International Congress on Burn Injuries, Stockholm, 1978.*

13. REITHNER, H.L., LAMKE, L-O. & NILSSON, G.E. The water vapour permeability of grafts and artificial membranes used in the treatment of burns. *5th International Congress on Burn Injuries, Stockholm, 1978.*

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17. NILSSON, G.E., TENLAND, T. & ÖBERG, P-Å. Laser Doppler flowmetry A non-invasive method for microvascular studies. *XII International conference on medical and biological engineering, Jerusalem, Israel, 1979.*

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19. LEWIS, D., HOLMSTRÖM, A., NILSSON, G.E., TENLAND, T. & ÖBERG,P-Å. Measurement of microcirculatory blood flow with a new non-invasive laser Doppler technique. II Experimental and applications. *La Jolla, California, USA. Microvascular Research, Vol 17, No 3, May 1979.*

20. LEWIS, D., HOLMSTRÖM, A., NILSSON, G.E., TENLAND, T., ÖBERG,P-Å. & LARSSON, J. Skeletal muscle trauma: Correlation of microcirculatory and biochemical changes. *Brit Microcirc Soc, 1979.*

21. ÖBERG, P-Å., HAMMARLUND, K., NILSSON, G.E. & SEDIN, G. Measurement of water exchange through the skin of newborn infants.*International Conference on Fetal and Neonatal PhysiologicalMeasurements, Biol Eng Soc, England, 1979.*

22. SEDIN, G., HAMMARLUND, K., NILSSON, G.E. & ÖBERG, P-Å. Evaporation of water from the skin of newborn infants. *International Conference on Fetal and Neonatal Physiological Measurements, Biol Eng Soc, Oxford, England, 1979.*

23. NILSSON, G.E., TENLAND, T. & ÖBERG, P-Å. Blodflödesmätning med laser Doppler teknik. *Läkarsällskapets riksstämma, 1979.*

24. LAMKE, L-O., NILSSON, G.E. & REITHNER, H.L. Kutana vätskeförluster vid förhöjd kroppstemperatur. *Sv Kir Förening, Vol XXXVII,1979.*

25. NILSSON, G.E., TENLAND, T. & ÖBERG, P-Å. Measurement of skin blood flow by laser Doppler flowmetry. *Biol Engng Soc 20th anniversary international conference on blood flow, theory and practice, London,England, 1980.*

26. LEWIS, D.H., HOLMSTRÖM, A., NILSSON, G.E., TENLAND, T. & ÖBERG, P-Å. Experiences with a new laser Doppler flowmeter for measurement of microcirculatory blood flow. *XII World Conference of Angiology,Athen, Greece, 1980.*

27. NILSSON, G.E., TENLAND, T. & ÖBERG, P-Å. Laser Doppler Flowmetry - new possibilities in the study of tissue blood flow. *V Nordic meeting in Biomed Engng, Linköping, 1981.*

28. TENLAND, T., NILSSON, G.E. & ÖBERG, P-Å. Laser Doppler Flowmetry -clinical applications of a new method for evaluating blood flow. *V Nordic meeting in Biomed Engng, Linköping, 1981.*

29. SALERUD, G., NILSSON, G.E., TENLAND, T. & ÖBERG, P-Å. Rhythmic vasomotion in human skin studied by laser Doppler flowmetry. *V Nordic meeting in Biomed Engng, Linköping, 1981.*

30. NILSSON, A.L., NILSSON, G.E. & ÖBERG, P-Å. Oscillatory phenomena in transepidermal water loss. *V nordic meeting in Biomed Engng, Linköping, 1981.*

31. NILSSON, G.E., TENLAND, T. & ÖBERG, P-Å. Laser Doppler flowmetry. *V Vascular symposium, London, England, 1981. (poster).*

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